Further insights into cardiovascular outcomes in diabetic and non-diabetic states: inhibition of sodium-glucose co-transporters

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Cardiovascular diseases are the leading cause of morbidity and mortality in the world. Diabetes increase heart disease related to death by two- to four-fold. SGLT2 inhibitors are new antidiabetic agents. The growing evidence of cardiovascular benefit of SGLT2 inhibitors independent of their effects on glycemic control is especially intriguing. Several clinical trials have shown that sotagliflozin (SGLT1-1/2 inhibitor) decreases body weight and reduces blood pressure in adults with T2D. A phase 3 study designed to evaluate cardiovascular outcomes of sotagliflozin is currently ongoing. Many pre-clinical studies were conducted to investigate the potential mechanisms involved in cardiovascular benefits of SGLT1 or SGLT2 inhibition with or without diabetes. Although multiple mechanisms have been proposed, there are still not

enough data to fully support the mechanisms of actions. This review aims to discuss the potential mechanisms involved in cardiovascular benefits of SGLT1 and SGLT2 inhibition in both diabetic and non-diabetic states.

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Introduction

Both type 1 and type 2 diabetes are chronic and complex diseases. Often times, patients suffer from several complications at the same time, among which cardiovascular (CV) events are the leading causes of morbidity and mortality. Hence, multi-targeted approach is required to manage the disease. Despite progresses of therapeutic armamentarium has been made, it is still difficult to tailor different treatment strategies to the need of a single patient. SGLT inhibitors are a class of new anti-diabetic agents. In human, SGLT2 is primarily expressed in kidney [1]. It has been reported that SGLT2 is responsible for more than 80% of glucose reabsorption in proximal tubule of nephron and the remaining filtered glucose load is reabsorbed by SGLT1 [2]. Growing evidences have proved that they are extremely effective and reliable in hyperglycemic control. Their glucose-lowering effect is independent of insulin. They decrease blood glucose by inhibiting sodium-glucose co-transporters. Furthermore, recent evidence of significant efficacy in improving CV outcomes in T2D patients through SGLT2 inhibition is very encouraging. A great deal of attention has been drawn into the research regarding its mechanism of action. EMPA-REG outcomes suggested that SGLT2 inhibition protected the heart through non-atherothrombotic mechanisms, mainly because of the rapid emergence of these benefits [3]. Several different theories have been proposed to explain the profound salutary effects of SGLT2 inhibitor on CV outcomes. It is

suggested that inhibition of SGLT2 decreases ventricular overload through its diuretic effects [4]. In addition, SGLT2 inhibitors may improve energy consumption in the heart, thereby result in improved cardiac efficiency and cardiac output [5,6]. It is also reported that SGLT2 may protect the heart through a direct effect on the myocardium [7]. Inhibition of SGLT2 can reduce cytoplasmic sodium and calcium level while increase mitochondrial calcium level [8]. Myocardial fibrosis is a hallmark of heart failure. Collagen deposition in myocardium result in decreased ventricular compliance and contractility. Researchers have demonstrated that inhibition of SGLT2 may have direct effect on cardiac fibroblast and decrease cardiac fibrosis [9]. Growing research interests in this area have provided us multiple lines of evidence regarding mechanisms involved in cardioprotective effects of SGLT2 inhibitors. However, there are still questions that remain unanswered. For example, SGLT2 receptors are not expressed in the heart [10], how do SGLT2 inhibitors exert direct effects in the heart? Secondly, since several mechanisms are independent of glucose-lowering effect of SGLT2 inhibitors, can SGLT2 inhibitors show CV benefits in patients without diabetes?

Unlike SGLT2, SGLT1 is highly expressed in small intestine compare to its expression in kidney. In addition, high level of SGLT1 is also found in human heart [11]. Recently, sotagliflozin (SGLT1/2 dual inhibitor) was filed for use of type 1 diabetes (T1D). Although Food and Drug Administration advisory committee has decided to

decline use of sotagliflozin for adult with T1D, a clinical trial designed to evaluate sotagliflozin on CV events in patients with T2D is ongoing. It is intriguing to compare CV outcomes of sotagliflozin vs. SGLT2 inhibitors in T2D patients. Because of the extra-renal function of SGLT1, inhibition of SGLT1 can potentially provide direct CV benefit. *In vivo* and *ex vivo* animal studies have suggested that inhibition of SGLT1 protects the heart against cardiac ischemia/reperfusion injury through decreased oxidative stress in the heart [12]. Further studies in CV benefits of sotagliflozin will provide us insights in mechanisms involved in cardioprotective effects of SGLT1 and 2 inhibitors. It is also possible that SGLT2 inhibitors exert CV benefits through inhibiting SGLT1 in the heart. In this review, we aim to discuss reported and ongoing SGLT1 and 2 trials and outline some of the potential mechanisms that may help us understand the cardioprotective benefits of SGLTs inhibition.

Completed clinical trials

A series of clinical trials have been completed worldwide to evaluate the effectiveness of CV outcomes in T2D patients treated with SGLT2 inhibitors. Table 1 summarized the key features of 4 important clinical trials. Empagliflozin CV Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) sponsored by Eli Lilly, was a multi-center, randomized, double blind, and placebo-controlled study of empagliflozin in patients with T2D and established CVD. Seven thousand sixty-four patients were recruited in this 4.6 years study. Sex was not balanced in this study with ~30% female vs. ~70% male. The mean ages of participant in all three different groups were ~63. Race/ethnicity was not included in the report. Empagliflozin was tested at two doses (10 and 25 mg daily) vs. placebo. Empagliflozin treatment effectively reduced HbA_{1c} (by 0.3%–0.5%). Researchers are particularly interested in this study because primary outcome from this study showed that empagliflozin significantly reduced major adverse CV events including death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke.

CANagliflozin CV Assessment Study sponsored by Janssen Research & Development, LLC was completed in December 2018. Canagliflozin was tested at two doses (100 and 300 mg) once daily via oral administration vs. placebo for 8 years. Four thousand three hundred thirty participants were recruited in this study. Sex was not balanced in this study with ~33% female vs. ~67% male. Seventy-four percent of the participants were white, 18% were Asian, 10% were Hispanic or Latino, and the rest were unknown. CV Events [major adverse cardiac events (MACE)] composed of CV death, non-fatal MI and non-fatal stroke. Canagliflozin 100 and 300 mg significantly reduced MACE vs. placebo (25% and 28% vs. 30%). Slight rise in low density lipoprotein and high density lipoprotein were observed at the end of the treatment.

Table 1 Cardiovascular outcomes of SGLT2 inhibitor therapy in type 2 diabetes patients

	Medication	N	History	Study design	Primary outcome measured	Result	Additional benefits
EMPA-REG	Empagliflozin	7020	T2D, high risk for CV events, BMI < 45	Multi-center, randomized, double-blind, placebo-controlled, open-label	3-point MACE (CV death, nonfatal MI, nonfatal stroke). Powered to assess noninferiority and superiority	Primary outcome: empagliflozin 10.5%, placebo 12.1%, hazard ratio (HR): 0.86 [95% confidence interval (CI): 0.74–0.99], $P < 0.001$	Shown decreased progression and incidence of CKD. Empagliflozin 12.7%, placebo 18.8%, hazard ratio: 0.61 (95% CI: 0.53–0.70), $P < 0.001$
DECLARE-TIMI58	Dapagliflozin	17,276	T2D, pre-existing CVD, history of hypertension	Multi-center, randomized, double-blind, placebo-controlled	3-point MACE-CV death, stroke and MI	Primary outcome: Dapagliflozin 8.8%, placebo 9.4%, HR: 0.93 (95% CI: 0.84–1.03), $P < 0.17$	Shown improvement in the composite renal secondary endpoint (end-stage renal disease, or renal or CV death) dapagliflozin 4.3%, placebo 5.6%, hazard ratio: 0.76 (95% CI: 0.67–0.87)
CANVAS	Canagliflozin	4331	T2D, history or high risk of CVD	Multi-center, randomized, double-blind, placebo-controlled	3-point MACE-CV death, stroke and MI	Primary outcome: Canagliflozin 26.93%, placebo 31.48%, HR: 0.86 (95% CI: 0.75–0.97), $P < 0.0001$	
CREDENCE	Canagliflozin	4401		Multi-center, randomized, double-blind, placebo-controlled	End-stage kidney disease (ESKD), doubling of serum creatinine, renal or CV death	Primary outcome: canagliflozin 43.2%, placebo 61.2% (HR: 0.70; CI: 0.59–0.82), $P = 0.00001$	

MACE, major adverse cardiac events.

1. EMPA-REG: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients.

2. DECLARE-TIMI58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events.

3. CANVAS: CANagliflozin cardiovascular Assessment Study.

4. CREDENCE: Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy.

All-cause mortality was slightly decreased in both canagliflozin 100 and 300 mg vs. placebo (4.7% and 4.6% vs. 5%). No significant differences were observed between canagliflozin and placebo regarding serious adverse events.

Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of CV Events (DECLARE-TIMI58) was carried out to determine the effect of dapagliflozin on cardiovascular outcomes when added to current background therapy in patients with type 2 diabetes with either established cardiovascular disease or CV risk factors. Dapagliflozin was tested at 10 mg once daily vs. placebo via oral administration. Participants were followed up to 6 years. Primary outcome measured including: (1) Time to first event included in the composite endpoint of CV death, MI, or ischemic stroke; (2) Time to first event included in the composite endpoint of CV death or hospitalization due to heart failure. All-cause mortality was measured as secondary outcome. Seventeen thousand one hundred nineteen participants were enrolled in the study. A few important findings from DECLARE are: (1) Compared Dapagliflozin significantly decreased rates of CV death or hospitalization for heart failure. (2) These CV benefits of Dapagliflozin were independent of ASCVD (all traditional risk factors) or prior history of heart failure. (3) No significant differences were observed between Dapagliflozin and placebo regarding adverse events.

Comparison of pharmacodynamic effects of sotagliflozin (SGLT1/2 dual inhibitor) and empagliflozin in T2D with Mild to Moderate Hypertension sponsored by Sanofi was completed in April 2019. Although the primary objective of this study was to compare the metabolic and gastrointestinal pharmacodynamics (PD) effects of 8 weeks treatment with sotagliflozin or empagliflozin, CV parameters were also measured as secondary outcomes. Echocardiography parameters including left ventricular ejection fraction and left ventricular end-diastolic diameter were measured. Results from this study may provide further information regarding the cardioprotective mechanisms involved in SGLT2 inhibition. It may also provide us future directions about research in this area.

CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and CV Outcomes in Participants with Diabetic Nephropathy) was designed to explore the potential benefits of SGLT2 inhibitor treatment in improving renal outcomes in type 2 diabetes patients. All the patients recruited in this study had an estimated glomerular filtration rate of 30 to <90 ml per minute per 1.73 m² of body-surface area and albuminuria [ratio of albumin (mg) to creatinine (g), >300 to 5000]. The median follow-up was 2.62 years. This study showed that canagliflozin group had a lower risk of CV death, MI, or stroke and hospitalization for heart failure.

Ongoing clinical trials

Fourteen clinical trials are currently ongoing or active with objective to study CV benefits of SGLT2 inhibitors.

Table 2 summarized the key features of nine important clinical trials. Different aspects as well as different treatment strategies are designed in these studies. GLP-1 agonist is another class of anti-diabetic drugs which have shown CV benefits. It has always been intriguing to see a comparison between these two different classes and their combination regarding CV effects. A study has been designed to fulfill this purpose. Since diuretic effect, decreased ventricular loading and potential effect on metabolism have been proposed to be involved in cardioprotective effects of SGLT2 inhibitors. Studies including 'SGLT2 inhibition in combination with diuretics in heart failure' and 'does dapagliflozin regress left ventricular hypertrophy in patients with T2D' are currently active. Results from studies including 'dapagliflozin, cardio-metabolic risk factors and T2D' and 'studies of empagliflozin and its CV, renal and metabolic effects' will give us further insights into the effect of SGLT2 inhibitors on metabolism in the heart.

As we mentioned before, SGLT1 is the only SGLT isoforms that expressed in the heart. 'Effect of sotagliflozin on cardiovascular and renal events in patients with T2D and moderate renal impairment who are at cardiovascular risk' and 'Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF Trial)' are currently ongoing. We may be able to find out whether or not SGLT1 inhibition is beneficial to the heart through these studies. Results of these studies can potentially revolutionize how heart failure is managed clinically.

Real-world retrospective observation studies

Three large real-world studies were carried out to evaluate the CV benefits of SGLT2 inhibitor treatment in type 2 diabetes patients. These studies evaluated outcomes similar in completed and on-going clinical trials. Results from these studies (Table 3) have shown that compared to other glucose-lowering agents, SGLT2 inhibitor treatment had better outcomes for all-cause mortality, hospitalization for heart failure, and MACE. These studies provided insight into class trends in CV outcomes of SGLT2 inhibitors.

In vivo, ex vivo, and in vitro studies

It is reported that canagliflozin can attenuate MI in both diabetic and non-diabetic heart. *Ex vivo* study was conducted in diabetic and non-diabetic rats. Four weeks of canagliflozin treatment resulted in decreased myocardial infarct size and increased cardiomyocytes survival in both diabetic and non-diabetic mice [13]. Downregulation of SGLT1 in *in vivo*, *ex vivo*, and *in vitro* mouse models protected mice hearts against myocardial ischemia/reperfusion injury [12]. These results suggest that inhibition of SGLTs is cardioprotective regardless of diabetic status. Multiple mechanisms were proposed regarding cardioprotective effects of SGLTs inhibition.

Table 2 On-going clinical trials assessing cardiovascular benefits of SGLT2 inhibitor therapy in type 2 diabetes patients

	Medication	N	History	Study design	Primary outcome measured	Result
SIMPLE	Empagliflozin	92	T2D, high cardiovascular risk, confirmed history of myocardial infarction	Randomized	Rb-82 PET and invasive hemodynamics	Ongoing
SCORED	Sotagliflozin	10 500	T2D	Multi-center, randomized, double-blind, placebo-controlled	Time to first MACE, time to cardiovascular death or HHF	Ongoing
EMPA-HEART VERTIS CV	Empagliflozin Ertugliflozin	97 8000	T2D, established cardiovascular disease T2D, high cardiovascular risk	Randomized Multi-center, randomized, double-blind, placebo-controlled	Left ventricular mass changes Time to first MACE	Ongoing Ongoing
SUGAR	Empagliflozin	130	T2D, heart failure	Randomized	LVESVI and left ventricular global longitudinal strain	ongoing
ERTU-GLS	Ertugliflozin	120	T2D, Stage B HF	Randomized	Global longitudinal strain (GLS)	Ongoing
SOLOIST-WHF Trial	Sotagliflozin	4000	T2D, HF	Multi-center, randomized, double-blind, placebo-controlled	CV death, HHF	Ongoing
EMPA Acute Heart Failure	Empagliflozin	56	T2D, acute HF	Randomized	Effect of empagliflozin on cardiac output in patients with acute heart failure	Ongoing
ELITE	Empagliflozin	100	T2D, stable coronary artery disease, global myocardial perfusion reserve (MPR) <2.5	Randomized	Percent change in MPR index	Ongoing

1. SIMPLE: SGLT-2 inhibitor and myocardial perfusion, function, and metabolism in T2DM patients at high cardiovascular risk.
2. SCORED: effect of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk.
3. EMPA-HEART: effects of empagliflozin on cardiac structure in patients with type 2 diabetes.
4. VERTIS CV: cardiovascular outcomes following ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease.
5. SUGAR: studies of empagliflozin and its cardiovascular, renal, and metabolic effects.
6. ERTU-GLS: effect of ertugliflozin on cardiac function in diabetes.
7. SOLOIST-WHF Trial: effect of sotagliflozin on cardiovascular events in patients with type 2 diabetes post-worsening heart failure.
8. EMPA acute heart failure: effect of empagliflozin on cardiac output in patients with acute heart failure.
9. ELITE: empagliflozin vs. sitagliptin therapy for improvement of myocardial perfusion reserve in diabetic patients with coronary artery disease.

Table 3 Cardiovascular benefits of SGLT2i treatment in patients with type 2 diabetes: real-world evidences

	Medication	N	History	Study design	Primary outcome measured	Result
EASEL	SGLT2 inhibitors (canagliflozin, empagliflozin, and dapagliflozin)	25,258	T2D and established CVD	propensity-matched population, retrospective cohort analysis using observational databases	Hospitalization for heart failure (HHF), all-cause mortality and MACE	Primary outcomes: SGL2 inhibitors 1.73%, non-SGLT2 inhibitor therapies 3.01%, hazard ratio: 0.57 (95% CI: 0.50–0.65).
CVD-REAL	SGLT2 inhibitors or "other glucose-lowering drugs" (oGLD)	309 056	T2D, with or without established CVD	propensity-matched population, retrospective cohort analysis using observational databases	HHF and MACE	SGL2 inhibitors showed overall 39% lower risk of heart failure hospitalization ($P < 0.001$), 51% reduction in total death ($P < 0.001$)
OBSERVE 4-D	SGLT2 inhibitors or non-SGLT2 inhibitor therapies	714,582	T2D, with or without established CVD	propensity-matched population, retrospective cohort analysis using observational databases	HHF and MACE	HHF: Canagliflozin non-SGLT2 inhibitors HR 0.39; 95% CI: 0.26–0.60; $P = 0.01$

1. EASEL: the evidence for cardiovascular outcomes with sodium-glucose co-transport-2 inhibitors in the real world.
2. CVD-REAL: cardiovascular events associated with SGLT2 inhibitors vs. other glucose-lowering drugs.
3. OBSERVE 4-D: a real-world meta-analysis of four observational databases.

Role of calcium

After exposing to high glucose culture medium for 14 days, hiPSC-derived cardiomyocytes showed increased SGLT1 expression. Empagliflozin treatment was able to decrease SGLT1 expression [14]. Diabetic patients without coronary artery disease can still develop ventricular dysfunction. This condition is known as diabetic cardiomyopathy. Calcium overload in cardiomyocytes in diabetic patients may play a central role in ventricular dysfunction. Inhibition of SGLT1 can potential lower sodium entry to cytoplasm and followed by decreased calcium cytosolic calcium concentration [15]. Seven days empagliflozin treatment was able to attenuate the altered calcium handling and restore contractility and relaxation of high-glucose treated cardiomyocytes, independent of the glycolytic capacity [14].

Role of oxidative stress

Increased oxidative stress is detected in diabetic hearts. Knockdown of SGLT1 in *in vitro* HL-1 cells (mouse atrium cardiomyocytes) protects the cells against hypoxia/reoxygenation (H/R) injury. Furthermore, mice with cardiomyocytes-specific knockdown of SGLT1 were resistant to both in-vivo and ex-vivo myocardial ischemia/reperfusion (I/R) injury [12]. Detailed mechanism studies suggested that knock down of SGLT1 resulted in decreased oxidative stress induced by both I/R and H/R through protein kinase C and NADPH oxidase 2 dependent mechanisms [12]. *In vivo* study conducted in diabetic KK-Ay mice showed that 8 weeks empagliflozin treatment via oral administration resulted in improved cardiac function, decreased myocardial oxidative stress as well as decreased myocardial fibrosis [16]. These results suggest that inhibition of SGLTs can decrease myocardial oxidative stress both with and without the presence of diabetes. It is reported that empagliflozin decreases oxidative stress through mitochondrial fission [17].

Role of eNOS

Acute canagliflozin treatment protects against myocardial ischemia/reperfusion injury in non-diabetic mice [18]. Five minutes pretreatment of canagliflozin before I/R was able to alleviate left ventricle systolic and diastolic dysfunction. Detailed mechanism study suggests that inhibition of SGLT2 increases endothelial nitric oxide synthase (eNOS) during I/R, thereby enhances endothelium-dependent vasorelaxation [18]. Empagliflozin is able to rescue diabetic myocardial microvascular injury by preserving cardiac microvascular barrier function and integrity, sustaining eNOS phosphorylation and endothelium-dependent relaxation [17]. Exposure of high glucose in endothelial cell results in increased SGLT1 and SGLT2 expression, decreased eNOS production and thereby decreased NO production [19]. Inhibition of SGLT1 and SGLT2 by LX-4211 (dual SGLT1/2 inhibitor) can reverse these effects.

Role of metabolism

Empagliflozin improves myocardial energy production by switching myocardial fuel metabolism away from glucose toward ketone bodies, which improves myocardial energy production [20]. Non-diabetic pig subjected to 2 hours ischemic injury or sham was treated with empagliflozin or placebo for 2 months. Empagliflozin treatment improved left ventricular systolic dysfunction, ameliorated adverse cardiac remodeling, and heart failure [20]. However, a different study performed in acute swine *in vivo* I/R model suggested that treatment of canagliflozin is cardioprotective independent of alterations in myocardial substrate utilization [21]. It is possible that long-term inhibition and short-term inhibition of SGLT2 have different effect on cardiac metabolism and energy production.

Role of fibrosis

It is documented that increased cardiac fibrosis and cardiac remodeling is present in diabetic hearts. Increased SGLT1 is observed in hypertrophic, ischemic, and diabetic cardiomyopathy in human hearts [22]. Myocardial I/R injury failed to induce interstitial fibrosis and cardiac remodeling in SGLT1 deficient mice [23]. Hypertrophic cardiomyopathy can be induced through transverse aortic constriction (TAC). TAC operation increased interstitial fibrosis in wild type mice but not in SGLT1 deficient mice. These results suggested increased SGLTs expressions are related to collagen deposition and cardiac fibrosis. Eight weeks of ipragliflozin treatment prevented LV hypertrophy and fibrosis in non-diabetic DS/obese rats without affecting plasma glucose levels. These findings suggest that SGLT2 inhibitors have a cardio-protective effect in non-diabetic patients with cardiomyopathy [24]. Four weeks treatment of dapagliflozin (selective SGLT2 inhibitor) results in decreased myofibroblast infiltration and cardiac fibrosis induced by ischemic injury [9]. Similarly, 4 weeks of phlorizin (dual SGLT1/2 inhibitor) are also able to decrease myofibroblast infiltration induced by ischemic injury [9].

SGLT2 inhibition and cardiovascular outcomes

No single mechanism of action can explain the favorable CV outcomes of SGLT2 inhibitors. Inhibition of SGLT2 can indirectly improve cardiac function through natriuresis followed by reduction of volume overload. However, how do SGLT2 inhibitors exert direct effects in heart when SGLT2 receptors are not expressed in this organ? Promising mechanisms including an improved oxygen supply to the failing heart via an increase of the hematocrit, a metabolic shift towards the consumption of more ketone bodies when other fuels like glucose fail in heart failure. Another interesting model of action for empagliflozin is to reduce CaMKII activity in ventricular myocytes, as suggested by Mustroph *et al.* [25]. Different empagliflozin has higher selectivity toward SGLT2 receptor over SGLT1. SGLT1 is highly expressed in the heart, in pathophysiological conditions including heart failure

and diabetes, expression of SGLT1 is further elevated in the heart [22]. As we mentioned before, it was reported that empagliflozin was able to decrease SGLT1 expression in hiPSC-derived cardiomyocytes [14]. Hence, it is intriguing to speculate that empagliflozin exerts some of the direct effects on the heart through the inhibition of CaMKII or SGLT1.

Summary and discussion

Results from different clinical trials and animal studies provided us a better understanding of mechanisms involved in cardioprotective effects of SGLTs inhibition in both diabetic and non-diabetic status. It appears that both SGLT1 and SGLT2 have significant roles in CV events. Stress conditions including ischemia, diabetes, and heart failure increase SGLT1 and two expression in the heart. Inhibition of SGLT1 protects the heart through decreased oxidative stress, improvement of eNOS activity, and reduction of cardiac fibrosis. Inhibition of SGLT2 protects the heart through natriuresis, metabolic shift, improved Ca^{2+} handling, and reduction of cardiac fibrosis. Inhibition of SGLTs have CV benefits far beyond glyce-mic control. Hence, it is highly possible that SGLT2 inhibitors have CV benefits in non-diabetic patients as well. Currently, empagliflozin is studied in patients with heart failure with or without T2D (EMPEROR-Reduced). Dapagliflozin is also being examined in patients with reduced ejection fraction (Dapa-HF). Sotagliflozin is now studied in heart failure patients after acute worsening of heart failure. Results from all these different studies will provide us many puzzle pieces of mechanisms involved in CV benefits of SGLTs inhibition, and eventually, we will have a whole picture.

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Conflicts of interest

There are no conflicts of interest.

References

- Sabolic I, Vrhovac I, Eror DB, Gerasimova M, Rose M, Breljak D, *et al.* Expression of Na^{+} -D-glucose cotransporter SGLT2 in rodents is kidney-specific and exhibits sex and species differences. *Am J Physiol Cell Physiol* 2012; **302**:C1174–C1188.
- Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30–50% of filtered glucose load in humans. *Diabetes* 2013; **62**:3324–3328.
- Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJ. SGLT2 inhibition and cardiovascular events: why did EMPA-REG outcomes surprise and what were the likely mechanisms? *Diabetologia* 2016; **59**:1333–1339.
- Verma S, McMurray JJV, Cherney DZL. The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. *JAMA Cardiol* 2017; **2**:939–940.
- Ferrannini E, Mark M, Mayoux E. Response to comment on Ferrannini *et al.* CV protection in the EMPA-REG OUTCOME trial: a 'thrifty substrate' hypothesis. *Diabetes care* 2016; **39**:1108–1114. *Diabetes Care* 2016; **39**:e226.
- Lopaschuk GD, Verma S. Empagliflozin's fuel hypothesis: not so soon. *Cell Metab* 2016; **24**:200–202.
- Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. *JAMA Cardiol* 2017; **2**:1025–1029.
- Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na^{+} through inhibition of the cardiac $\text{Na}^{+}/\text{H}^{+}$ exchanger in rats and rabbits. *Diabetologia* 2017; **60**:568–573.
- Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med* 2017; **104**:298–310.
- Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia* 2018; **61**:2108–2117.
- Zhou L, Cryan EV, D'Andrea MR, Belkowski S, Conway BR, Demarest KT. Human cardiomyocytes express high level of Na^{+} /glucose cotransporter 1 (SGLT1). *J Cell Biochem* 2003; **90**:339–346.
- Li Z, Agrawal V, Ramratnam M, Sharma RK, D'Auria S, Sincoular A, *et al.* Cardiac sodium-glucose co-transporter 1 (SGLT1) is a novel mediator of ischemia/reperfusion injury. *Cardiovasc Res* 2019 Epub ahead of print.
- Lim VG, Bell RM, Arjun S, Kolatsi-Joannou M, Long DA, Yellon DM. SGLT2 inhibitor, canagliflozin, attenuates myocardial infarction in the diabetic and nondiabetic heart. *JACC Basic Transl Sci* 2019; **4**:15–26.
- Ng KM, Lau YM, Dhandhan V, Cai ZJ, Lee YK, Lai WH, *et al.* Empagliflozin ameliorates high glucose induced-cardiac dysfunction in human IPSC-derived cardiomyocytes. *Sci Rep* 2018; **8**:14872.
- Banerjee K, Ghosh RK, Kamatam S, Banerjee A, Gupta A. Role of ranolazine in cardiovascular disease and diabetes: exploring beyond angina. *Int J Cardiol* 2017; **227**:556–564.
- Li C, Zhang J, Xue M, Li X, Han F, Liu X, *et al.* SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. *Cardiovasc Diabetol* 2019; **18**:15.
- Zhou H, Wang S, Zhu P, Hu S, Chen Y, Ren J. Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. *Redox Biol* 2018; **15**:335–346.
- Sayour AA, Korkmaz-Icöz S, Loganathan S, Ruppert M, Sayour VN, Oláh A, *et al.* Acute canagliflozin treatment protects against *in vivo* myocardial ischemia-reperfusion injury in non-diabetic male rats and enhances endothelium-dependent vasorelaxation. *J Transl Med* 2019; **17**:127.
- Khemais-Benkhiat S, Belcastro E, Idris-Khodja N, Park SH, Amoura L, Abbas M, *et al.* Angiotensin II-induced redox-sensitive SGLT1 and 2 expression promotes high glucose-induced endothelial cell senescence. *J Cell Mol Med* 2019 Epub ahead of print.
- Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, *et al.* Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol* 2019; **73**:1931–1944.
- Baker HE, Kiel AM, Luebbe ST, Simon BR, Earl CC, Regmi A, *et al.* Inhibition of sodium-glucose cotransporter-2 preserves cardiac function during regional myocardial ischemia independent of alterations in myocardial substrate utilization. *Basic Res Cardiol* 2019; **114**:25.
- Banerjee SK, McGaffin KR, Pastor-Soler NM, Ahmad F. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. *Cardiovasc Res* 2009; **84**:111–118.
- Hirose M, Matsushita N, Ishida N, Ibi M, Saito M. [Roles of sodium-glucose cotransporter 1 (SGLT1) in the induction of cardiac remodeling]. *Yakugaku Zasshi* 2018; **138**:939–943.
- Takasu T, Takakura S. Effect of ipragliflozin, an SGLT2 inhibitor, on cardiac histopathological changes in a non-diabetic rat model of cardiomyopathy. *Life Sci* 2019; **230**:19–27.
- Mustroph J, Wagemann O, Lucht CM, Trum M, Hammer KP, Sag CM, *et al.* Empagliflozin reduces Ca^{2+} /calmodulin-dependent kinase II activity in isolated ventricular cardiomyocytes. *ESC Heart Fail* 2018; **5**:642–648.